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(54) Title: COMPOSITIONS AND USES OF ET743 FOR TREATING CANCER

(57) Abstract

ET743 is used in the preparation of a medicament for the treatment of the human body for cancer.

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# COMPOSITIONS AND USES OF ET743 FOR TREATING CANCER

The present invention relates to the treatment of cancers.

## Background of Invention

Cancer comprises a group of malignant neoplasms that can be divided into two categories, carcinoma, comprising a majority of the cases observed in the clinics, and other less frequent cancers, which include leukemia, lymphoma, central nervous system tumours and sarcoma. Carcinomas have their origin in epithelial tissues while sarcomas develop from connective tissues and those structures that had their origin in mesoderm tissues. Sarcomas can affect, for instance, muscle or bone and occur in the bones, bladder, kidneys, liver, lung, parotid or spleen.

Cancer is invasive and tends to metastasise to new sites. It spreads directly into surrounding tissues and also may be disseminated through the lymphatic and circulatory systems. Many treatments are available for cancer, including surgery and radiation for localised disease, and drugs. However, the efficacy

of available treatments on many cancer types is limited, and new, improved forms of treatment showing clinical benefit are needed. This is especially true for those patients presenting with advanced and/or metastatic disease. It is also true for patients relapsing with progressive disease after having been previously treated with established therapies for which further treatment with the same therapy is mostly ineffective due to acquisition of resistance or to limitations in administration of the therapies due to associated toxicities.

Chemotherapy plays a significant part in cancer treatment, as it is required for treatment of advanced cancers with distant metastasis and often helpful for tumor reduction before surgery, and many anti-cancer drugs have been developed based on various modes of action.

The ecteinascidins are marine alkaloids and some of them possess potent *in vitro* antitumour activity. Several ecteinascidins have been reported previously in the patent and scientific literature.

For example, U.S. Patent N° 5,089,273 describes novel compositions of matter extracted from the tropical marine invertebrate, *Ecteinascidia turbinata*, and designated therein as ecteinascidins 729, 743, 745, 759A, 759B and 770. These

compounds are useful as antibacterial and / or antitumour agents in mammals.

U.S. Patent N° 5,256,663 describes pharmaceutical compositions comprising matter extracted from the tropical marine invertebrate, *Ecteinascidia turbinata*, and designated therein as ecteinascidins, and the use of such compositions as antibacterial, anti-viral, and/or antitumour agents in mammals.

U.S. Patent N° 5,478,932 describes ecteinascidins isolated from the Caribbean tunicate *Ecteinascidia turbinata*, which provide *in vivo* protection against P388 lymphoma, B16 melanoma, M5076 ovarian sarcoma, Lewis lung carcinoma, and the LX-1 human lung and MX-1 human mammary carcinoma xenografts.

U.S. Patent N° 5,654,426 describes several ecteinascidins isolated from the Caribbean tunicate *Ecteinascidia turbinata*, which provide in vivo protection against P388 lymphoma, B16 melanoma, M5076 ovarian sarcoma, Lewis lung carcinoma, and the LX-1 human lung and MX-1 human mammary carcinoma xenografts.

U.S. Patent N°. 5,721,362 describes a synthetic process for the formation of ecteinascidin compounds and related structures.

Further background is to be found illustratively in: Corey, E.J., J. Am. Chem. Soc., 1996, 118 pp. 9202-9203; Rinehart, et al., Journal of National Products, 1990, "Bioactive Compounds from Aquatic and Terrestrial Sources", vol. 53, pp. 771-792; Rinehart et al., Pure and Appl. Chem., 1990, "Biologically active natural products", vol 62, pp. 1277-1280; Rinehart, et al., J. Org. Chem., 1990, "Ecteinascidins 729, 743, 745, 759A, 759B, and 770: Potent Antitumour Agents from the Caribbean Tunicate *Ecteinascidia turbinata*", vol. 55, pp. 4512-4515; Wright et al., J. Org. Chem., 1990, "Antitumour Tetrahydroisoquinoline Alkaloids from the Colonial Ascidian *Ecteinascidia turbinata*", vol. 55, pp. 4508-4512; Sakai et al., Proc. Natl. Acad. Sci. USA 1992, "Additional antitumour ecteinascidins from a Caribbean tunicate: Crystal structures and activities *in vivo*", vol. 89, 11456-11460; Science 1994, "Chemical Prospectors Scour the Seas for Promising Drugs", vol. 266,pp. 1324; Koenig, K.E., "Asymmetric Synthesis", ed. Morrison, Academic Press, Inc., Orlando, FL, vol. 5, 1985,p. 71; Barton, et al., J. Chem Soc. Perkin Trans., 1, 1982, "Synthesis and Properties of a Series of Sterically Hindered Guanidine Bases", pp. 2085; Fukuyama et al., J. Am Chem. Soc., 1982, "Stereocontrolled Total Synthesis of (+) – Saframycin B", vol. 104,pp. 4957; Fukuyama et al., J. Am Chem Soc., 1990, "Total Synthesis of (+) – Saframycin A", vol. 112, p. 3712; Saito, et al., J. Org. Chem., 1989, "Synthesis of Saframycins. Preparation of a Key Tricyclic Lactam Intermediate to Saframycin A", vol. 54, 5391; Still, et al., J. Org. Chem., 1978, "Rapid Chromatographic

Technique for Preparative Separations with Moderate Resolution", vol. 43, p. 2923; Kofron, W.G.; Baclawski, L.M., J. Org. Chem., 1976, vol. 41, 1879; Guan et al., J. Biomolec. Struc. & Dynam., vol. 10 pp. 793-817 (1993); Shamma et al., "Carbon-13 NMR Shift Assignments of Amines and Alkaloids", p. 206 (1979); Lown et al., Biochemistry, 21, 419-428 (1982); Zmijewski et al., Chem. Biol. Interactions, 52, 361-375 (1985); Ito, CRC CRIT. Rev. Anal. Chem., 17, 65-143 (1986); Rinehart et al., "Topics in Pharmaceutical Sciences 1989" pp. 613-626, D. D. Breimer, D.J. A. Cromwelin, K.K. Midha, Eds., Amsterdam Medical Press B.V., Noordwijk, The Netherlands (1989); Rinehart et al., "Biological Mass Spectrometry," 233-258 eds. Burlingame et al., Elsevier Amsterdam (1990); Guan et al., Jour. Biomolec. Struct. & Dynam., vol. 10 pp. 793-817 (1993); Nakagawa et al., J. Amer. Chem. Soc., 111: 2721-2722 (1989); Lichter et al., "Food and Drugs from the Sea Proceedings" (1972), Marine Technology Society, Washington, D.C.1973, 117-127; Sakai et al., J. Amer. Chem. Soc. 1996, 118, 9017; García-Rocha et al., Brit. J. Cancer, 1996, 73: 875-883; and Pommier et al., Biochemistry, 1996, 35: 13303-13309.

In particular, ecteinascidin 743 has been found also to exhibit promising action when tested in animal models, as, for example, when evaluated against xenografts of breast cancer, non-small cell lung, melanoma and ovarian cancer.

A paper on in vitro antitumour activity of the novel marine agent, Ecteinascidin-743 (ET-743, NSC-648766) against human tumours explanted from patients, Annals of Oncology, 9: 981-987, 1998, is typical of the in vivo reports. The authors conclude from their data that continuous or protracted exposure may enhance activity. In the same issue of that journal at pages 989-993, a paper on in vitro schedule-dependency of myelotoxicity and cytotoxicity of Ecteinascidin 743 (ET-743) concludes that prolonged exposure might represent the best schedule of administration.

## Summary of Invention

We have developed a method to treat human patients with ET743 leading to clinical improvement.

## Embodiments of the Invention

Thus, the present invention provides a method of treating any mammal, notably a human, affected by cancer which comprises administering to the affected individual a therapeutically effective amount of ET743, or a pharmaceutical composition thereof.

The present invention also relates to pharmaceutical preparations, which contain as active ingredient ET743, as well as the processes for their preparation.

Examples of pharmaceutical compositions include liquid (solutions, suspensions or emulsions) with suitable composition for intravenous administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds.

Administration of the compounds or compositions of the present invention is by intravenous infusion. We prefer that infusion times of up to 72 hours are used, more preferably 2 to 24 hours, with either about 3 or about 24 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be around 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 1 to 6 weeks. Further guidance is given later in this text.

The correct dosage of the compound will vary according to the particular formulation, the mode of application, and the particular *situs*, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compound ET743 and compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

a) drugs with antimitotic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);

b) antimetabolite drugs (such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);

c) alkylating agents or nitrogen mustards (such as nitrosoureas, cyclophosphamide or ifosphamide);

d) drugs which target DNA such as the antracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;

e) drugs which target topoisomerases such as etoposide;

f) hormones and hormone agonists or antagonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuprorelin, goserelin, cyprotrone or octreotide;

g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;

h) alkylating drugs such as platinum drugs (cis-platin, carbonplatin, oxaliplatin, paraplatin) or nitrosoureas;

i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;

j) gene therapy and antisense agents;

k) antibody therapeutics;

l) other bioactive compounds of marine origin, notably the didemnins such as aplidine;

m) steroid analogues, in particular dexamethasone;

n) anti-inflammatory drugs, including nonsteroidal agents (such as acetaminophen or ibuprofen) or steroids and their derivatives in particular dexamethasone; and

o) anti-emetic drugs, including 5HT-3 inhibitors (such as gramisetron or ondasetron), and steroids and their derivatives in particular dexamethasone.

The present invention also extends to the compounds of the invention for use in a method of treatment, and to the use of the

compounds in the preparation of a composition for treatment of cancer.

Patient responses have been observed in clinical trials with ET-743, demonstrating usefulness of the method of treatment.

Phase I clinical studies and pharmacokinetic analysis demonstrate that ET-743 presents a positive therapeutic window with manageable toxicity in the range of dosage required for clinical efficacy in the treatment of cancer patients.

The method consists of administration of drug by intravenous infusion over a period of 72 hrs or less at the recommended dose level (RD) with or without combination with other therapeutic agents.

ET-743 is supplied and stored as a sterile lyophilized product, consisting of ET 743 and excipient in a formulation adequate for therapeutic use, in particular a formulation containing mannitol and a phosphate salt buffered to an adequate pH.

A preferred formulation, which shows improved stability at higher storage temperature, is one obtained from 1000 ml of 0.9% sodium chloride or other suitable infusion vehicle, 250 μg of ET-743 with 250 mg of mannitol, 34 mg of monopotassium phosphate

and phosphoric acid to adjust to a pH between 4.00 and 6.00, with 4.80 being the preferred pH. The product is lyophilized and stored in the cold, between +4°C and –20°C and protected from light until use.

Preparation of the reconstituted solution is performed under aseptic conditions by adding distilled water in the amount of 5ml for every 250 μg of ET-743 and shaking for a short time to dissolve the solids.

Preparation of the infusion solution is also performed under aseptic conditions by withdrawing the reconstituted solution volume corresponding to dosage calculated for each patient, and slowly injecting the required reconstituted solution volume into an infusion bag or bottle containing between 100 and 1000 ml of 0.9% sodium chloride solution, after which the whole is homogenised by slow manual shaking. The ET-743 infusion solution should be administered intravenously, as soon as possible, within 48 hours after preparation. PVC and polyethylene infusion systems, as well as clear glass are preferred container and conduit materials.

The administration is performed in cycles, in the preferred application method, an intravenous infusion of ET734 is given to the patients the first week of each cycle, the patients are allowed to

recover for the remainder of the cycle. The preferred duration of each cycle is of either 3 or 4 weeks; multiple cycles can be given as needed. The drug may also be administered each of the first days of each cycle. Dose delays and/or dose reductions and schedule adjustments are performed as needed depending on individual patient tolerance of treatments, in particular does reductions are recommended for patients with higher than normal serum levels of liver transaminases or alkaline phosphatase, or bilrubin.

The Recommended Dose (RD) is the highest dose which can be safely administered to a patient producing tolerable, manageable and reversible toxicity according to the Common Toxicity Criteria established by the National Cancer Institute, (USA) with no more than 2 out of 6 patients presenting any dose limiting toxicities (DLT). Guidelines for cancer therapy frequently call for administration of chemotherapeutic agents at the highest safe dose at which toxicity is manageable in order to achieve maximum efficacy (DeVita, V.T. Jr., Hellman, S. and Rosenberg, S.A., Cancer: Principles and Practice of Oncology, 3rd ed., 1989, Lipincott, Philadelphia).

DLTs for ET743 using this method of treatment were determined in clinical studies to be myelosuppression and malaise. These studies established a recommended dose level of 1500 microgram per m2 of body surface area for 24hr infusions or 1650 microgram per m2 body surface area for 3 hr infusions. Doses of 1800

microgram per m2 or above resulted in too large a fraction of patients presenting DLT and thus were determined to be too toxic for safe administration

Whereas a case of a breast cancer response reported in June 98 was observed at a dose level of 1800 microgram/ m2, a level considered unsafe at any rate on infusion because 2 out of 4 patients presented severe dose limiting toxic responses. Another previously reported case involved a response in a melanoma patient after a 1 hr infusion, which method does not allow reaching the recommended dose level without dose limiting thrombocytopenia and fatigue.

ET-743 can be safely administered at a dosage level at or below the Recommended Dose (RD).

In particular intravenous infusion over 24hr at a dose level between 500 and 1500 microgram per m2 of body surface area, preferably, between 1000 and 1500 microgram per m2 of body surface area, the latter being the RD for this schedule as determined in clinical trials ea.

In particular intravenous infusion is suitably performed over 3 hr at a dose level between 500 and 1650 microgram per m2 of body surface area, preferably, between 1000 and 1650 microgram per

m2 of body surface area, the latter being the RD for this schedule as determined in clinical trials .

Other forms of treatment include intravenous infusion over 72hr at the RD for this schedule of 1050 microgram per m2 of body surface area.

An alternative procedure is an intravenous infusion over 5 consecutive days, 24hr daily, at the RD for this schedule of 1625 microgram per m2 of body surface area.

When ET 743 is used in combination with other therapeutic agents, the dosages of both agents may need to be adjusted.

Previously the only biological responses reported to the administration of ET743 had been observed in animal or *in vitro* models, known to be notoriously inaccurate concerning their usefulness to predict responses in human patients, or in human patients in experimental settings where an effective, safe method of treatment was unavailable (either the dosage used was a toxic dose significantly elevated over the recommended dose or the administration schedule was not appropriate).

In clinical trials using the method of this invention, appropriate plasma levels were achieved in patients at RD, and most

importantly, objectively measurable responses demonstrated evidence of clinical benefit to patients.

Definitions for patient responses are adopted from WHO Common Toxicity Criteria and the responses determined following standard medical practice in the field.

Objective responses were obtained in patients with advanced and/or metastatic cancers refractory to previous treatments, which included soft tissue, bone and gastrointestinal stromal sarcoma, breast cancer and melanoma. Evidence of activity, using a variety of suboptimal schedules which has also been observed in advanced ocular melanoma and mesothelioma, and a positive clinical marker response in ovarian cancer suggests the method of this invention will be useful in the treatment of these diseases as well.

In particular treatment with this method has shown responses in cancer patients with advanced and/or metastatic disease, which exhibited progressive disease after having been previously treated with established therapies.

A preferred method of this invention therefore involves identifying cancer patients who have been treated for cancer, particularly patients who have received chemotherapy, and treating them with ET743.

In particular treatment with this method has also shown responses in patients with sarcomas including soft tissue , bone and gastrointestinal stromal sarcomas. In particular treatment with this method has shown responses in patients with soft tissue sarcomas In particular treatment with this method has shown responses in patients with bone sarcomas. In particular treatment with this method has shown responses in patients with gastrointestinal stromal sarcomas. In particular treatment with this method has shown responses in patients with breast cancers.

The table, Figure 1, shows responses observed with this method of treatment.

The invention is further illustrated by the following examples which relate to clinical trials in humans.

Example 1

Data was analyzed from trials with 24 h iv continuous infusion of ET 743 every 3 or 4 weeks at 1500 $\mu g/m^2$
Pharmacokinetics of ET-743 are monitored in all patients during the first cycle of therapy to assess interpatient variability and possible correlations with clinical activity or toxicity

Patient population:

16 advanced/metastatic soft tissue sarcoma (STS) patients
12 soft tissue sarcoma patients with no prior chemotherapy treatments
8 advanced/metastatic gastrointestinal stromal tumor (GIST) patients.

Safety/Toxicities observed:

Tolerabilty of treatment was very good.
Nausea essentially eliminated by use of dexamethasone as a prophylactic anti emetic
Myelosuppression
Temporary/asymptomatic transaminitis
Fatigue

Data showed no significant differences with early phase I data

Efficacy

- 6 out of 10 evaluable STS patients without any prior chemotherapy treatment have exhibited stable disease or minor responses after 2 cycles of therapy,

- 4 out of 12 evaluable STS patients with prior chemotherapy treatment have exhibited stable disease or minor responses after 2 cycles of therapy,
- preliminary evidence of activity was observed in liposarcoma, leiomyo sarcoma, and synovial sarcoma.

Example 2

Data was analyzed from a trial with 24 h iv continuos infusion of ET 743 every 3 weeks on 20 pretreated advanced/metastatic breast cancer patients, at a dose level of 1500 $\mu g/m^2$.

Characteristics of patient population:

20 women,
all presenting measurable disease and progressing at study entry
age 33 to 64 years (median 50 yrs)
performance status 0-1 (ECOG criteria)
minimum number of involved organs:2 (range 1-6)
disease sites:

| | |
|---|---|
| cutaneous | 12 (60%) |
| liver | 10 (50%) |
| bone | 9 (45%) |
| lymph nodes | 6 (30%) |
| pleuro pulmonary | 6 (30%) |

| | |
|---|---|
| Minimum number of prior chemotherapy treatments | 2 (1-6) |
| Patients previously treated with Anthracyclines | 20 |
| Patients previously treated with Taxanes | 16 |
| Patients resistant to Anthracyclines and Taxanes | 5 |
| Patients resistant to Taxanes only | 2 |
| Patients resistant to Anthracyclines only | 3 |

Safety/toxicities:

Total number of cycles administered 56

minimum number of cycles per patient 2 (range 1-8)

Number of grade 3 or 4 toxicities reported per cycle.

| | |
|---|---|
| Neutropenia | 25 (50%) |
| Thrombocytopenia | 4 (2%) |
| Reversible transaminitis | 34 (60%) |
| Asthenia (grade 2/3) | 13 (23%) |

Data showed no significant differences with early phase I data

Efficacy

On 16 evaluable patients, Two partial responses were observed (pleuropulmonary and thoracic skin involvement) lasting 3.5 and over 2 months on patients without primary resistance to either pretreatment drug. Six patients achieved disease stabilization

(over 2, 3, 3, over 3, 4.5 and over 6 months) including two with sustained decrease in CA 15-3 a marker for this disease.

Example 3

Data was analyzed from a trial with 24 h iv continuos infusion of ET 743 every 3 weeks on 20 pretreated advanced/metastatic soft tissue sarcoma patients, with all except two patients being treated at a dose level of 1500 $\mu g/m^2$

Characteristics of patient population:

39 patients /22 female
35 Soft tissue sarcoma (STS)
3 osteosarcoma (OS)
1 Ewing sarcoma (ES)

22 patients had bulky disease at study entry, with 56% of disease progression under prior regime
age 16 to 71 years (median 45 yrs)
performance status 0 (0-2) (ECOG criteria)

Minimum number of prior chemotherapy treatments 2 (1-7)

Most patients had received as prior chemotherapy treatments Anthracyclines and alkylators

Safety/toxicities:

Total number of cycles administered 137
minimum number of cycles per patient 2 (range 1-12)
Number of grade 3 or 4 toxicities reported per cycle.

| | |
|---|---|
| Neutropenia | 34%, with 6.5% febrile |
| Thrombocytopenia | 5% |
| Acute, reversible transaminitis | 44% |
| Asthenia (grade 2/3) | 13 (23%) |

Data showed no significant differences with early phase I data

Efficacy

On 34 evaluable patients,
4 partial responses (11.7%) were observed, two of which became post surgical complete response
3 minor responses were observed, one of which became post surgical complete response 11 disease stabilizations, most of which lasting 3 months or more

Responses were observed in various histological types, including 2 out of 3 osteo sarcomas, in all disease sites, including visceral

metastases, in bulky and non bulky disease, and in anthracycline refractory and non refractory tumours.

Claim

1. The use of ET743 in the preparation of a medicament for the treatment of the human body for cancer.

2. A pharmaceutical formulation comprising ET743 for intravenous infusion to treat a human cancer.

3. A method of treating cancer in a human patient which comprises administering ET743.

4. A method of treating advanced and / or metastatic, previously treated cancer in a human patient which comprises administering ET743.

5. A method of treating cancer resistant or refractory to other treatments in a human patient which comprises administering ET743.

6. A method of treating sarcoma in a human patient which comprises administering ET743.

7. A method of treating soft tissue sarcoma in a human patient which comprises administering ET743.

8. A method of treating bone sarcoma in a human patient which comprises administering ET743.

9. A method of treating breast cancer in a human patient which comprises administering ET743.

10. A method of treating cancer in a human patient which comprises administering a dose of ET743 between 1000 and 1500 micrograms per m2 of body surface area by intravenous infusion over a period of 24hrs given in multiple cycles of 3 to 4 weeks each with a single administration of the drug on the first day of each cycle.

11. A method of treating cancer in a human patient which comprises administering a dose of ET743 between 1000 and 1650 micrograms per m2 of body surface area by intravenous infusion over a period of 3hrs given in multiple cycles of 3 to 4 weeks each with a single administration of the drug on the first day of each cycle.

| Sched. | Pts | Dose | RD* | Cycles | Tumor Type | Previous Chem. Lines | Response | Time to progression (months) |
|---|---|---|---|---|---|---|---|---|
| 1h | 40 | 585 | 1000 | 10 | Melanoma | - | pCR | 29+ |
| 3h | 32 | 1500 | 1650 | 10 | Leiomyosarcoma | 1 | CR | 12 |
| | | 1650 | | 13+ | Colon Stromal Sarcoma | 1 | PR | 10+ |
| | | 1650 | | 5+ | Gastric Stromal Sarcoma | 1 | MR | 4+ |
| 24h | 52 | 1500 | 1500 | 5 | Osteosarcoma | 4 | PR | 2 |
| | | 1500 | | 12 | Liposarcoma | 2 | PR | 15+ |
| | | 1800 | | 3 | Breast | 2 | PR | 3 |
| dx5 | 42 | 325x5 | 1625 | 6 | Leiomyosarcoma | 1 | MR (27%) | 4 |
| | | 325x5 | | 7 | Ovarian | 7 | MR+fall CA 125 | 6 |
| 72h | 21 | 1200 | 1050 | 6 | Mesothelioma | 1 | MR (41%) | 5 |
| | | 1200 | | 4 | Ocular Melanoma | - | Mixed R | 2 |
| | Total Pts 187 | | | | | | | |

# INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/GB 00/01857

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, BIOSIS, EMBASE, MEDLINE, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| P,X | WO 99 51238 A (UNIV ILLINOIS)<br>14 October 1999 (1999-10-14)<br>page 3, paragraph 1<br>claims 8,11-15 | 1-11 |
| P,X | WO 99 58125 A (PHARMA MAR SA ;FLORIANO PABLO (ES); REYMUNDO ISABEL (ES); GARCIA G) 18 November 1999 (1999-11-18)<br>page 2, line 12 - line 17 | 1-11 |
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| | -/-- | |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 21 August 2000 | 05/09/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Bonzano, C |

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Inter ›nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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| X | "ET743" DRUGS OF THE FUTURE, vol. 22, no. 11, 1997, page 1279 XP002145352 the whole document --- | 1-11 |
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Information on patent family members

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| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
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